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BACKGROUND OF THE INVENTION

A. Field of the Invention

The present invention relates generally to a computer-implemented system and method for analyzing data from nuclear magnetic resonance measurements, whereby the data contains at least one relaxation signal of a sample. More particularly, the presentinvention relates to a nuclear magnetic resonance tomograph and to a method for analyzing data from nuclear magnetic resonance measurements wherein at least one relaxation signal of a sample is determined.

B. Description of the Related Art

Nuclear magnetic resonance (NMR) is used to obtain a contrast image of an object or spectroscopic information about a substance. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) make it possible to examine regional hemodynamics *in vivo* with changes in blood volumes and blood states, as well as changes in the metabolism as a function of brain activity. See S. Posse *et al.*, Functional Magnetic Resonance Studies of Brain Activation; Seminars in Clinical Neuropsychiatry, Vol. 1, No. 1., pp. 76-88 (1996).

In medical research there is a need to acquire information about brain activity by means of measurements of blood flow or changes in the concentration of deoxyhemoglobin (DOH). Neuronal activation is shown by an increase of the blood flow into activated regions of the brain, whereby a drop occurs in the concentration of DOH. DOH is a paramagnetic substance that reduces the magnetic field homogeneity and thus accelerates the signal relaxation. If the DOH concentration drops due to brain activity that triggers blood flow, then the signal relaxation in the active regions of the brain is modulated primarily due to the excitation ofhydrogen protons in water. Brain activity localization is made possible by conducting an examination with functional

NMR methods that measure the NMR signal with a time delay (i.e., echo time). This is also referred to as a susceptibility-sensitive measurement. The biological mechanism of action is known as the BOLD (**B**lood **O**xygenation **L**evel **D**ependence) effect. In susceptibility-sensitive magnetic resonance measurements at a field strength of a static magnetic field of, for example, 1.5 Tesla, the BOLD effect leads to fluctuations of image brightness of up to 10% in activated regions of the brain. Besides the endogenous contrast agent DOH, other contrast agents can also occur that cause a change in the susceptibility. NMR imaging methods select slices or volumes that yield a measurement signal under appropriate irradiation with high-frequency pulses and under magnetic gradient fields. This measurement signal is digitized and stored in a two-dimensional or three-dimensional field in a computer. A two-dimensional or three-dimensional Fourier transform based upon the raw data reconstructs the desired image information.

A reconstructed slice image consists of pixels (picture elements), and a volume data set consists of voxels (volume elements). A pixel is a two-dimensional picture element that may be in the shape of, for example, a square. A voxel is a three-dimensional volume element that may be in the shape of, for example, a cube which, for metrological reasons, does not exhibit any sharp boundaries. The dimensions of a pixel are typically about 1 mm^2, and the dimensions of a voxel are typically about 1 mm^3. The geometries and dimensions of pixels and voxels, however, may vary.

Since experiments have shown that it is never possible to assume a strictly two-dimensional plane in the case of slice images, the term voxel is often employed because it takes into consideration the fact that the image planes extend into the third dimension.

By comparing the measured signal course in every pixel with the time course of a model function, a stimulus-specific neuronal activation can be detected and spatially localized. A

stimulus can be, for example, a somatosensorial, acoustic, visual or olfactory stimulus as well as a mental or motor task. The model function or the model time series describes the anticipated signal change of the magnetic resonance signal resulting from neuronal activation. These can be derived, for example, by means of empirical rules from a paradigm of the experiment in question. The essential aspect is to consider a time delay of the model function with respect to the paradigm (i.e., sluggish reaction of the blood flow in response to neuronal activation).

Depiction of brain activation by activation images acquired from nuclear spin tomographic data has been performed. The activation images can be computed and displayed in real time, that is, a data set can be converted into an image before the next data set is measured, wherein the time interval is typically 1 to 3 seconds. Computation and reproduction of activation images in real time are described in U.S. Patent No. 5,657,755, wherein the activation images have a high resolution in time and space.

Another conventional activation images method is disclosed in the articles by P. Jezzard *et al.*, Proc. SMRM, p. 1392 (1993); B. Biswal *et al.*, MRM 34, p. 537 (1995); and P. Purdon *et al.*, Proc. ISMRM, p. 253 (1998). This method uses a measuring signal and a paradigm of the measurement, wherein both signals undergo a Fourier transform.

All of the above-mentioned conventional methods analyze the similarity between the paradigm signal and the measured data signal. Thus, there is a need in the art for a method for analyzing NMR data that overcomes the deficiencies of the related art.

SUMMARY OF THE INVENTION

The present invention solves the problems of the related art by providing a computer-implemented system and method that separates NMR data into at least two parts that are

differently dependent on an echo time T_E.

In accordance with the purpose of the invention, as embodied and broadly described herein, the present invention includes a computer-implemented system that performs a fast spectroscopic imaging method that detects the changes in the NMR signal relaxation using a time constant $T_2^* = \frac{1}{R_2^*}$ at several points in time following excitation. The spectroscopic imaging method of the present invention is preferably an echo-planar imaging method, and more preferably a repeated, two-dimensional echo-imaging method that repeatedly uses two-dimensional echo-planar image encoding. Spatial encoding takes place within the shortest possible time span that is repeated several times during one signal decay and preferably ranges from 20 ms to 100 ms. The repetition of the echo-planar encoding during one signal decay depicts the course of the signal decay in the sequence of reconstructed individual images. An echo-planar method useful for the present invention is EPI (Echo-Planar-Imaging), and, more preferably, TURBO-PEPSI (Proton Echo Planar Spectroscopic Imaging).

The number of images that are encoded during the signal decay is dependent upon the relaxation time and the encoding time Δt for a single image. Preferably, a computer is used to analyze data from nuclear magnetic resonance tomography, wherein the data contains at least one relaxation signal of a sample. The computer-implemented method of the present invention separates the data into parts that are dependent on an echo time T_E and into at least one part that is not dependent on the echo time T_E, whereby the signals that are dependent on an echo time T_E are acquired as activation signals. The computer may include an analyzing means (e.g., a microprocessor) that performs the method of the present invention.

Several components of a function to be examined can be ascertained with the present invention by determining the signals that have a different dependence on the echo time T_E. Thus,

it is possible with the present invention to separate an amplitude δ_0 from a time constant T_2^* and/or from a noise signal g.

Further in accordance with the purpose of the invention, as embodied and broadly described herein, the present invention relates to a nuclear magnetic resonance tomograph that includes at least one computer performing the method of the present invention.

Preferably, the method of the present invention acquires intensity values of the measured data for identical echo times in at least two different recordings of the relaxation signal and subsequently acquires a dependence of the intensity values on the echo time T_E, wherein the relaxation signal is separated into parts having a different dependence on the echo time T_E. Preferably, the relaxation signal is divided into a part that is dependent on the echo time T_E and into at least one part that is not dependent on the echo time T_E, wherein the part that is dependent on the echo time T_E is acquired as an activation signal.

It is especially advantageous for at least one detected signal to be proportional to $T_E \exp(-T_E / T_2^*)$, whereby the value of T_2^* is determined particularly by means of a preferably separate fit procedure on the basis of the same data. T_2^* may be calculated with the following formula:

$$S = S_0 \exp(-T_E / T_2^*) + g,$$

wherein the statistical fluctuations ΔT_2^* are determined.

In a preferred embodiment of the present invention, the following calculations are performed by the computer-implemented method of the present invention: a standard deviation $\sigma(\Delta T_2^*)$; a quotient $\sigma(\Delta T_2^*) / T_2^*$ to be formed and acquired as a measure of an activity; a statistical deviation of an initial intensity S_0;a standard deviation $\sigma(S_0)$; a quotient $\sigma(S_0) / S_0$; a

statistical fluctuation of a noise signal g; and a standard deviation σ(g).

Moreover, the computer-implemented method of the present invention preferably acquires the recorded data in at least a two-dimensional field, whereby a field axis (DTE) acquires echo times T_E and whereby another field axis (DTR) reproduces repetitions of excitations at a time interval T_R. It is particularly advantageous for $\sigma(\Delta T_2^*)$ and σ(g) to be determined by means of the following steps:

(i) adaptation of signals averaged over the other field axis (DTR) to an exponential decay as a function of the first field axis (DTE) and determination of S_0 and T_2^*;

(ii) calculation of $\sigma(\Delta S_0)$, $\sigma(\Delta T_2^*)$ and σ(g) for several voxels and different T_E, followed by averaging of these values over at least one region of interest (ROI);

(iii) adaptation of

$$\frac{\sigma(\Delta S)}{S_0} = \left\{\left[\left(\frac{T_E}{T_s^*}\right)^2\left(\frac{\sigma\left(\Delta T_2^*\right)}{T_2^*}\right)^2 + \left(\frac{\sigma\left(\Delta S_0\right)}{S_0}\right)^2 - 2\frac{T_E}{T_2^*}\frac{\left(\Delta S_0 \Delta T_2^*\right)}{S_0 T_2^*}\right]\varepsilon^{-2T_E/T_2^*} + \left(\frac{\sigma(g)}{S_0}\right)^2\right\}; \text{ and}$$

(iv) determination of σ(ΔS) / S_0 as a function of T_E. It is also particularly advantageous for the expression $< \Delta S_0 \Delta T_2^* >= 0$ to be used for the adaptation of $\sigma(\Delta S_0)/S_0$.

Further scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will become more fully understood from the detailed description given hereinbelow and the accompanying drawings which are given by way of illustration only, and thus are not limitative of the present invention, and wherein:

Figure 1 is a schematic diagram showing a multi-echo sequence with several measuring sequences, each of which follows a spin excitation (*) and involves the acquisition of various echo times T_E;

Figure 2 is a schematic diagram showing a method involving the separate preparation of data for each of the echo times;

Figure 3 are graphs showing an experimental differential signal of a functional relaxation time change in a selected picture element as a function of the measuring time following a signal excitation;

Figure 4 are graphs showing ΔS from various voxels averaged over a few ROIs as a function of T_E for two representative persons; and

Figure 5 are actual images, wherein the upper image shows detection of brain activation in four steps using a conventional imaging method and the lower image shows detection of brain activation using the method of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following detailed description of the invention refers to the accompanying drawings. The same reference numbers in different drawings identify the same or similar elements. Also, the following detailed description does not limit the invention. Instead, the scope of the

invention is defined by the appended claims and equivalents thereof.

Figure 1 depicts a multi-echo sequence with several measuring sequences, each of which follows a spin excitation (*) and involves the acquisition of various echo times T_E. The measuring sequences of the multi-echo sequence were determined by means of the TURBO-PEPSI method. Each of the measuring sequences contains twelve echo signals with echo times that lie between 12 and 213 ms. The echo times were each acquired in the form of a time interval ΔT_E of 18.3 ms. The values of the echo times and the time intervals are adapted to the speed of the data processing. With further improvements in scanner technology, it will be possible to raise the number of echo signals and to shorten the time intervals ΔT_E.

Figure 2 is a schematic diagram showing how differing measuring sequences are used to acquire a signal at a first echo time or at a second or subsequent echo time.

In the curve depicted in Figure 3, a measuring signal $\sigma(S)$ has been acquired as a function of the echo time. Figure 3 further shows a fit procedure that serves to divide the measuring signal $\sigma(S)$ into components that are dependent on T_2^* and into noise that is not dependent on T_E. The measuring signal $\sigma(S)$ consists of a part that is dependent on anamplitude S_0, of a part that is dependent on a relaxation time T_2^*, and of a constant noise signal g.

The computer-implemented system and method of the present invention differentiates between activation signals and noise by analyzing the course of time of the measured data and/or their statistical distribution.

The analysis method of the present invention may be checked experimentally with, for example, nuclear spin tomographic examinations of the brains of test subjects. A source of light, preferably a matrix of light-emitting diodes (LED), may be positioned directly in front of the face of the test subjects and then excited to emit flash signals. The frequency of excitation may

be eight Hz. The effect of the signal flashes may be exerted over a time interval — synchronized with the carrier signal from a scanner — of several seconds (e.g., five seconds), which is followed by a rest interval of approximately the same duration. The source of light may be a Vision 1.5 Tesla, full-body scanner made by Siemens Medical Systems of Erlangen, Germany, with a magnetic field gradient of 25 mT/m. Such a scanner is able to switch over gradient fields within about 600 μs. TURBO-PEPSI (Proton Echo Planar Spectroscopic Imaging) may be employed as the spectroscopic imaging method. Data adaptation may be performed according to the exponential function $S = S_0 e^{-T_E/T_2^*}$, and making use of a non-linear least-square-fit.

The differentiation between activation and noise with multi-echo fMRI will now be described. The detection of physiological noise (caused, for example, by a heart beat) requires a stationary frequency spectrum for adequate temporal resolution and prior knowledge about the spatial and temporal characteristics of the noise. The present invention provides a new method for differentiating between BOLD-related variations and other fluctuations of the MR signal (caused, for example, by thermal noise) without any prior knowledge of a stimulation paradigm. The method of the present invention is based upon a single-shot-multi-echo sequence similar to the TURBO-PEPSI technique described in S. Posse *et al.*, PROC. ISMRM, p. 299 (1998), the disclosure of which is incorporated by reference herein in its entirety.

Following signal excitation, the method of the present invention records the relaxation behavior at equidistant time intervals T_E. This is repeated several times at time intervals of T_R seconds. The signal of each voxel forms a two-dimensional field with the echo times T_E in one direction (DTE) and with the repetitions at the time interval T_R in the other direction (DTR). The relaxation is assumed to be monoexponential, $S = S_0 \exp(-T_E / T_2^*) + g$, with a hardware-dependent noise g that can be considered white noise in both domains, DTE and DTR. The

values S_0 and T_2^* are constant in DTE but vary in DTR. The value of S_0 may vary, for example, due to hardware instabilities or blood flow effects, and the value of T_R may vary, for example, due to test subject stimulation. Variations in T_2^* indicate changes in the local blood flow. In the case of relatively small changes ΔS_0 and ΔT_2^*, the signal changes may be formulated as follows:

$$\frac{\Delta S}{S_0} = \left\{ \left[\left(\frac{T_E}{T_s^*} \right)^2 \left(\frac{\sigma(\Delta T_2^*)}{T_2^*} \right)^2 + \left(\frac{\sigma(\Delta S_0)}{S_0} \right)^2 - 2 \frac{T_E}{T_2^*} \frac{(\Delta S_0 \Delta T_2^*)}{S_0 T_2^*} \right] \varepsilon^{-2T_E/T_2^*} + \left(\frac{\sigma(g)}{S_0} \right)^2 \right\}^{1/2} \quad [1]$$

wherein <A> and σ(A) correspond to the mean value and to the standard deviation of a quantity A in DTR. Further analysis depends on the actual magnitude of the terms used in Equation [1].

Under experimental conditions, ΔS_0 is negligible in the resting and activation phases (except in the sagital sinus). The quantities $\sigma(\Delta T_2^*)$ and σ(g) may be determined as follows: (i) adaptation of the signal averaged over the DTR to the monoexponential decay as a function of DTE in order to determine S_0 and T_2^*; (ii) calculation of $\sigma(\Delta T_2^*)$ and σ(g) for each voxel and each T_E and averaging these values over the region of interest (ROI); (iii) adaptation of Equation [1] with $\Delta S_0=0$ to these values as a function of T_E. This is possible because local brain activation is shown by an increase of T_2^*, which displays a characteristic T_E-dependence proportional to $T_E e^{-T_R/T_2^*}$, whereas the value of the white noise does not depend on T_E (as shown in the Figures). The T_E-dependence of the signal outside the brain is approximated by a constant. In order to validate the method of the present invention, the quantity of white noise is compared to the noise outside the brain, taking into consideration that σ(g) is reduced outside the brain. For a Gaussian distribution, this reduction factor is 0.6028.

Visual stimulation experiments involving four healthy test subjects were carried out employing a Siemens Vision-1.5-Tesla scanner. A multi-layer TURBO-PEPSI sequenceacquired

twelve EPI images having a matrix size of 64 x 32 pixels and a pixel size of 3 x 6 mm^2 from a single FID, 90° flip angle at echo times ranging from 12 to 228 ms. A conventional correlation analysis was carried out with the Stimulate software package, a GUI (Graphical User Interface) based fMRI (functional Magnetic Resonance Imaging) analysis software package, with the use of a boxcar reference vector.

Figure 4 shows ΔS from various voxels averaged over a few ROIs as a function of T_E for two representative persons. The variability of all values over ROIs was small (e.g., 10% to 20%). The ROIs were located in the visual cortex (vc), in the motor cortex (mc), in the white matter (wm), and outside the brain, circumventing areas outside the brain that are characterized as phantom images, (out). The filter results from Equation [1] are compiled in Table 1. Wherever the abbreviated ROI designations are followed by the number of voxels between parentheses, the mean correlation coefficient is normalized over a ROI, $\sigma(g)$ of the ROI outside the brain, to the mean S_0 of the inner ROIs and the errors in all values are defined as a standard deviation.

Table 1

ROI	ξ	$\sigma(\Delta T_2^*)/T_2$ (%)	$\sigma(g)/S_0$ (%)
vc (20)	0.62 ± 0.21	4.3 ± 0.1	0.75 ± 0.05
mc (20)	-0.11 ± 0.14	0.26 ± 0.16	0.79 ± 0.05
wm (21)	-0.009 ± 0.19	-0.001 ± 5	0.93 ± 0.07
out (21)	-0.19 ± 0.11	not fitted	0.66 ± 0.01
vc (28)	0.67 ± 0.12	3.6 ± 0.1	0.42 ± 0.07
mc (32)	-0.22 ± 0.14	-0.6 ± 0.8	0.72 ± 0.06
wm (32)	-0.29 ± 0.06	-0.4 ± 1.2	0.64 ± 0.06
out (38)	-0.12 ± 0.25	not fitted	0.45 ± 0.01

For all persons, the value of $\sigma(\Delta T_2^*)/T_2^*$ in the activated voxels was significantly increased, whereas there was no significant deviation from zero in the non-activated voxels. This is why this value has a determining character with a negligible stochastic component. Consequently, $\sigma(\Delta T_2^*)/T_2^*$ is as suitable as an indicator of regional brain activity as the

correlation coefficients of a conventional correlation analysis. In contrast to conventional correlation analysis, however, $\sigma(\Delta T_2^*)/T_2^*$ displays brain activity for any desired stimulation course, so that it is not necessary to have knowledge of a paradigm. The slight variability of this value over the ROIs indicates that the results for individual voxels are similar to those presented here. This allows the creation of $\sigma(\Delta T_2^*)/T_2^*$ maps. The level of the T_E-independent white noise is very low, and thus, stems from the hardware. The S_0 noise is so small that a more precise examination of the S_0 noise is difficult in view of the white noise that is present.

The computer-implemented system and method of the present invention thus differentiates between an activation, especially brain activation and noise, whereby no correlation analysis is required. Naturally, the present invention may also be employed in combination with other correlation analyses such as, for example, a calculation of correlation coefficients, Z scores, or the application of a t-test, to check the results obtained in this manner. However, with the present invention, there is no need for a correlation analysis with two different measurements, one with stimulation and the other without stimulation. For comparison purposes, however, it is possible to include a correlation analysis in which correlation coefficients between the course of time of the stimulator ("reference vector") and the signal changes in pixels of the image are ascertained. High values for the correlation coefficient ascertained in this process may be regarded as an activity indicator and reproduced as additional information in slice images or volume images in the case of a graphic representation of the measured data.

The present invention is particularly well-suited for applications in areas where complicated activations occur. For this reason, the computer-implemented system and method of the present invention are especially suitable for analyzing higher cognitive brain functions, such

as emotions, memory, and imagination.

The present invention provides numerous advantages over conventional methods and systems, including: optimization of the measuring sensitivity for a quantitative measurement of the relaxation time and of the qualitative relaxation time change; use of imaging with the highest possible bandwidth (shortest encoding time) for the smallest spatial distortion possible; and maximum measuring sensitivity by measuring an optimal number of encodings following signal excitation.

The system and method of the present invention may be used in real time measurements in order to directly analyze the relaxation changes. In addition, the system and method of the present invention are particularly versatile. It has been proven to be practical to employ a summation or, even more advantageously, a weighted summation which, in comparison to a curve adaptation, can be done faster and without any loss of the measuring sensitivity. A summation, or a weighted summation, are advantageous because they constitute particularly reliable analysis methods.

All of the test subjects exhibited a strong activation in the primary visual cortex (V_1) and in the neighboring regions. The changes observed in the functional signal measured with TURBO-PEPSI amount to up to 10%, depending on the relaxation time T_2^*, the position, and the test subject in question. The excitation exhibited a maximum in the vicinity of $T_E = T_2^*$. A comparison of EPI and TURBO-PEPSI images with T_E = 72.5 ms revealed very similar activation images. The gain in sensitivity is particularly advantageous for real time measurements since a change in the relaxation may be effectively ascertained, even with just a few measured values. In summary, the multi-echo detection of the differential signal of the present invention provides optimal sensitivity for various magnetic field strengths. Furthermore,

the invention can be utilized in echo-planar imaging (EPI), phase-encoded imaging methods, as well as spectroscopic imaging methods.

It will be apparent to those skilled in the art that various modifications and variations can be made in the computer-implemented system and method of the present invention and in construction of the system and method without departing from the scope or spirit of the invention. As an example, the computer-implemented system and method of the present invention may also be used to examine other samples of either living or non-living material, other than the human brain.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.